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Shimizu, et al.	:	
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For Solid Preparation		

DECLARATION

I, Kiyomi Nakano, technical translator, declare that I am a citizen of Japan, residing at 2-72-204, Kurakuen-ichibancho, Nishinomiya, Hyogo, Japan; that I am competent to make English translations and have had considerable experience in that work; that the attached is true translation into the English language of the Japanese Patent Application No. 9-136724 (136724/1997).

I, the undersigned, declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed this 4th day of July, 2000

Kiyomi Nakano

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[Title of the Invention] Solid Preparation

[Claims]

[Claim 1]

A solid preparation which comprises (i) a pharmaceutically active ingredient, (ii) a water-soluble sugar alcohol, and (iii) low-substituted hydroxypropylcellulose having hydroxypropoxyl group contents of 7.0 to 9.9 percent by weight.

[Claim 2]

A solid preparation according to claim 1, wherein the water-soluble sugar alcohol is erythritol.

[Claim 3]

A solid preparation according to claim 1, wherein the water-soluble sugar alcohol is incorporated in an amount of 5 to 97 weight parts per 100 weight parts of the solid preparation.

[Claim 4]

A solid preparation according to claim 1, wherein the low-substituted hydroxypropylcellulose having hydroxypropoxyl group contents of 7.0 to 9.9 percent by weight is incorporated in an amount of 3 to 50 weight parts per 100 weight parts of the solid preparation.

[Claim 5]

A solid preparation according to claim 1, which is capable of buccal disintegration or dissolution.

[Claim 6]

Use of low-substituted hydroxypropylcellulose having hydroxypropoxyl group contents of 7.0 to 9.9 percent by weight for the manufacture of a pharmaceutical preparation capable of buccal disintegration or dissolution.

[Detailed Description of the Invention]

[Field of industrial application]

The present invention relates to a solid

preparation, especially a preparation capable of buccal disintegration or dissolution, having characteristics of fast disintegration or dissolution in the oral cavity even without water.

[Prior art]

There has been a demand for development of a pharmaceutical preparation capable of buccal disintegration or dissolution, which can be, if necessary, administered readily even without water, by aged people and children anywhere or anytime. Examples of prior art references disclosing such preparation are shown below.

JP-A H9(1997)-48726 discloses rapid buccal dissolution type preparations comprising a drug and a material wetting in a mouldable way on humidifying and retaining a shape after moulding and drying. Such material is exemplified by sugars, sugar alcohols, and water-soluble polymers.

JP-A H5(1993)-271054 discloses a method of producing a rapid buccal dissolution type tablets comprising a pharmacologically active ingredient and sugars.

JP-A H9(1997)-71523 discloses tablets with rapid disintegration in the oral cavity which comprise a drug, crystalline cellulose, low-substituted hydroxypropylcellulose and a lubricant.

However, these prior art references nowhere disclose a solid preparation comprising a pharmaceutically active ingredient, a water-soluble sugar alcohol, and low-substituted hydroxypropylcellulose having hydroxypropoxyl group contents of 7.0 to 9.9 percent by weight.

[Problems to be solved by the invention]

There has been a demand for development of a solid

preparation which exhibits excellent buccal disintegration and dissolution and also an appropriate strength (hardness) such that the solid preparation never disintegrates or suffers damage in the course of the production steps or distribution stages.

[Means of solving the problem]

The present invention relates to a solid preparation comprising (1) a pharmaceutically active ingredient, (2) a water-soluble sugar alcohol, and (3) low-substituted hydroxypropylcellulose having hydroxypropoxyl group contents of 7.0 to 9.9 percent by weight; and use of low-substituted hydroxypropylcellulose having hydroxypropoxyl group contents of 7.0 to 9.9 percent by weight for the manufacture of a pharmaceutical preparation capable of buccal disintegration or dissolution.

The pharmaceutically active ingredient to be used in the present invention may be in any optional form, for example, a solid, powder or granular, crystalline, oily or solution form.

As the pharmaceutically active ingredient, for instance, there may be mentioned one or more ingredients selected from the group consisting of nourishing and health-promoting agents, antipyretic-analgesic-antiinflammatory agents, antipsychotic drugs, antianxiety drugs, antidepressants, hypnotic-sedatives, spasmolytics, central nervous system affecting drugs, cerebral metabolism ameliolators, antiepileptics, sympathomimetic agents, gastrointestinal function conditioning agents, antacids, antiulcer agents, antitussive-expectorants, antiemetics, respiratory stimulants, bronchodilators, antiallergic agents, dental buccal drugs, antihistamines, cardiotonics,

antiarrhythmic agents, diuretics, hypotensive agents, vasoconstrictors, coronary vasodilators, peripheral vasodilators, antihyperlipidemic agents, cholagogues, antibiotics, chemotherapeutic agents, antidiabetic agents, drugs for osteoporosis, skeletal muscle relaxants, antidinics, hormones, alkaloid narcotics, sulfa drugs, antipodagrics, anticoagulants, anti-malignant tumor agents, etc.

Examples of the nourishing and health-promoting agents include vitamins such as vitamin A, vitamin D, vitamin E (d-α-tocopherol acetate, etc.), vitamin B_1 (dibenzoylthiamine, fursultiamine hydrochloride, etc.), vitamin B2 (riboflavin butyrate, etc.), vitamin B_6 (pyridoxine hydrochloride, etc.), vitamin C (ascorbic acid, sodium L-ascorbate, etc.), vitamin B_{12} (hydroxocobalamin acetate, etc.), etc.; minerals such as calcium, magnesium and iron; proteins, amino acids, oligosaccharides, crude drugs, etc.

Examples of the antipyretic-analgesic-antiinflammatory agents include aspirin, acetaminophen, ethenzamide, ibuprofen, diphenhydramine hydrochloride, dl-chlorpheniramine maleate, dihydrocodeine phosphate, noscapine, methylephedrine hydrochloride, phenylpropanolamine hydrochloride, caffeine, anhydrous caffeine, serratiopeptidase, lysozyme chloride, tolfenamic acid, mefenamic acid, diclofenac sodium, flufenamic acid, salicylamide, aminopyrine, ketoprofen, indomethacin, bucolole, pentazocine, etc.

Examples of the antipsychotic drugs include chlorpromazine, reserpine, etc.

Examples of the antianxiety drugs include alprazolam, chlordiazepoxide, diazepam, etc.

Examples of the antidepressants include imipramine, maprotiline, amphetamine, etc.

Examples of the hypnotic-sedatives include estazolam, nitrazepam, diazepam, perlapine, phenobarbital sodium, etc.

Examples of the spasmolytics include scopolamine hydrobromide, diphenhydramine hydrochloride, papaverine hydrochloride, etc.

Examples of the central nervous system affecting drugs include citicoline, rotirenine, etc.

Examples of the cerebral metabolism ameliolators include idebenone, meclofenoxate hydrochloride, etc.

Examples of the antiepileptics include phenytoin, carbamazepine, etc.

Examples of the sympathomimetic agents include isoproterenol hydrochloride, etc.

Examples of the gastrointestinal function conditioning agents include stomachic-digestives such as diastase, saccharated pepsin, scopolia extract, cellulase AP3, lipase AP, cinnamon oil, etc.; intestinal function controlling drugs such as perperine hydrochloride, resistant lactic acid bacterium, Lactobacillus bifidus, etc.

Examples of the antacids include magnesium carbonate, sodium hydrogen carbonate, magnesium aluminometasilicate, synthetic hydrotalcite, precipitated calcium carbonate, magnesium oxide, etc.

Examples of the antiulcer agents include lansoprazole, omeprazole, rabeprazole, pantoprazole, famotidine, cimetidine, ranitidine hydrochloride, etc.

Examples of the antitussive-expectorants include chloperastine hydrochloride, dextromethorphan hydrobromide, theophylline, potassium guaiacolsulfonate, guaifenesin, codeine phosphate, etc.

Examples of the antiemetics include diphenidol hydrochloride, metoclopramide, etc.

Examples of the respiratory stimulants include levallorphan tatrate, etc.

Examples of the bronchodilators include theophylline, salbutamol sulfate, etc.

Examples of the antiallergic agents include amlexanox, seratrodast, etc.

Examples of the dental buccal drugs include oxytetracycline, triamcinolone acetonide, chlorhexidine hydrochloride, lidocaine, etc.

Examples of the antihistamines include diphenhydramine hydrochloride, promethazine, isothipendyl hydrochloride, dl-chlorpheniramine maleate, etc.

Examples of the cardiotonics include caffeine, digoxin, etc.

Examples of the antiarryhythmic agents include procainamide hydrochloride, propranolol hydrochloride, pindolol, etc.

Examples of the diuretics include isosorpide, furosemide, etc.

Examples of the hypotensive agents include delapril hydrochloride, captopril, hexamethonium bromide, hydralazine hydrochloride, lapetalol hydrochloride, manidipine hydrochloride, candesartan cilexetil, methyldopa, etc.

Examples of the vasoconstrictors include phenylephrine hydrochloride, etc.

Examples of the coronary vasodilators include carbocromen hydrochloride, molsidomine, perapamil hydrochloride, etc.

Examples of the peripheral vasodilators include cinnarizine, etc.

Examples of the antihyperlipidemic agents include cerivastatin sodium, simvastatin, pravastatin, etc.

Examples of the cholagogues include dehydrocholic acid, trepiputone, etc.

Examples of the antibiotics include cephem antibiotics such as cefalexin, amoxicillin,

pipmecillinam hydrochloride, cefotiam dihydrochloride, cefozopran hydrochloride, cefmenoxime hydrochloride, cefsluodin sodium, etc.; synthetic antibacterials such as ampicillin, cyclacin, sulbenicillin sodium, nalidixic acid, enoxacin, etc.; monobactam antibiotics such as carumonam sodium; penem antibiotics, carbapenem antibiotics, etc.

Examples of the chemotherapeutic agents include sulfamethizole hydrochloride, thiazosulfone, etc.

Examples of the antidiabetic agents include tolbutamide, voglibose, pioglitazone hydrochloride, troglitazone, etc.

Examples of the drugs for osteoporosis include ipriflavone, etc.

Examples of the skeletal muscle relaxants include methocarpamol, etc.

Examples of the antidinics include meclizine hydrochloride, cimenhydrinate, etc.

Examples of the hormones include riothynine sodium, dexmethasone sodium phosphate, prednisolone, oxendolone, leupororelin acetate, etc.

Examples of the alkaloid narcotics include opium, morphine hydrochloride, ipecac, oxycodone hydrochloride, opium alkaloids hydrochlorides, cocaine hydrochloride, etc.

Examples of the sulfa drugs include sulfanilamide, sufamethizole, etc.

Examples of the antipodagrics include allopurinol, colchicine, etc.

Examples of the anticoagulants include dicoumarol, etc.

Examples of the anti-malignant tumor agents include 5-fluorouracil, uracil, mitomycin, etc.

The pharmaceutically active ingredients may be coated, by the per se known method, for masking the

taste and odor or for enteric dissolution or sustained release. The coating material that can be employed includes, for instance, enteric coating polymers such as cellulose acetate phthalate, methacrylic acid copolymer L, methacrylic acid copolymer LD, methacrylic acid copolymer S, hydroxypropylmethylcellulose phthalate, hydroxypropylmethylcellulose acetate succinate, carboxymethylethylcellulose, etc.; gastric coating polymers such as polyvinylacetal diethylaminoacetate, aminoalkyl methacrylate copolymer, etc.; water-soluble polymers such as hydroxypropylcellulose, hydroxypropylmethylcellulose, etc.; water-insoluble polymers such as ethylcellulose, aminoalkyl methacrylate copolymer RS, ethylacrylate methylmethacrylate copolymer, etc.; wax, etc.

The above pharmaceutically active ingredients are used, for instance, in an amount of 0.01 to 70 weight parts, preferably 0.02 to 50 weight parts, more preferably 0.05 to 30 weight parts, per 100 weight parts of a solid preparation.

Among the above pharmaceutically active ingredients, nourishing and health-promoting agents, antipyretic-analgesic-antiinflammatory agents, hypnotic-sedatives, central nervous system affecting drugs, gastrointestinal function conditioning agents, antiulcer agents, antitussive-expectorants, antiallergic agents, antiarrhythmic agents, diuretics, hypotensive agents, vasoconstrictors, coronary vasodilators, antihyperlipidemic agents, antidiabetic agents, drugs for osteoporosis, skeletal muscle relaxants and antidinics are preferably employed.

In the present invention, a water-soluble sugar alcohol means a water-soluble sugar alcohol which needs

water in an amount of less than 30 ml when 1 g of a water-soluble sugar alcohol is added to water and dissolved within about 30 minutes at 20 C° by strongly shaking every 5 minutes for 30 seconds.

As the water-soluble sugar alcohol, sorbitol, mannitol, maltitol, reduced starch saccharide, xylitol, reduced paratinose or erythritol is employed. Two or more of these water-soluble sugar alcohols can be used as a mixture in a given ratio.

The water-soluble sugar alcohol is preferably mannitol, xylitol or erythritol, especially preferably erythritol. As erythritol, one that is produced by fermentation with yeasts using glucose as the starting material, and that has a particle size of at most 50 mesh is used. Such erythritol is available as a product on the market such as a product manufactured by Nikken Chemical Co., Ltd., etc.

The water-soluble sugar alcohol is used, for instance, in an amount of 5 to 97 weight parts, preferably 10 to 90 weight parts, per 100 weight parts of a solid preparation. If the amount of the water-soluble sugar alcohol to be used is too much compared with such ranges, sufficient strength of a preparation can not be obtained. On the contrary, the amount of the water-soluble sugar alcohol to be used is too small, sufficient buccal disintegration or dissolution can not be obtained. Both of these are not preferable.

The hydroxypropoxyl group contents (hereafter also referred to as HPC group contents) of a low-substituted hydroxypropylcellulose employed in the present invention range from 7.0 to 9.9 percent by weight.

Examples of the low-substituted hydroxypropylcellulose having HPC group contents of 7.0 to 9.9 percent by weight include LH-22, LH-32, and

mixtures thereof. These are available as a product on the market such as a product manufactured by Shin-Etsu Chemical Co., Ltd.

The low-substituted hydroxypropylcellulose having HPC group contents of 7.0 to 9.9 percent by weight is used in an amount of 3 to 50 weight parts, preferably 5 to 40 weight parts, per 100 weight parts of a solid preparation. If the amount of the low-substituted hydroxypropylcellulose to be used is too much compared with such ranges, sufficient buccal disintegration or dissolution can not be obtained. On the contrary, the amount of the low-substituted hydroxypropylcellulose to be used is too small, sufficient strength of a preparation can not be obtained. Both of these are not preferable.

The solid preparation of the present invention is useful especially as a preparation which is capable of buccal disintegration or dissolution, and administered without water or together with water.

The dosage forms of a solid preparation of the present invention includes tablets, granules, fine granules, etc., with preference given to tablets.

Unless buccal disintegration or dissolution, or strength of a preparation is interfered with, a solid preparation of the present invention may further contain a variety of additives which are commonly employed in the manufacture of preparations in general dosage forms. The amount of such additives to be used is one commonly employed in the manufacture of preparations in general dosage forms.

Such additives include, for instance, binders, acids, foaming agents, artificial sweeteners, flavorants, lubricants, colorants, stabilizers, etc.

Examples of the binders include hydroxypropylcellulose, hydroxypropylmethylcellulose, crystalline cellulose, pregelatinized starch, polyvinylpyrrolidone, gum arabic powder, gelatin, pullulan, etc. The use of crystalline cellulose as the binders provides a solid preparation which exhibits more excellent strength of a preparation while retaining excellent buccal disintegration and dissolution.

Examples of the acids include citric acid, tartaric acid, malic acid, etc.

Examples of the foaming agents include sodium hydrogen carbonate, etc.

Examples of the artificial sweeteners include saccharin sodium, dipotassium glycyrrhizinate, aspartame, stevia, thaumatin, etc.

Examples of the flavorants include lemon, lemon lime, orange, menthol, etc.

Examples of the lubricants include magnesium stearate, sucrose fatty acid ester, polyethyleneglycol, talc, stearic acid, etc.

Examples of the colorants include various food colorants (e.g. Food Yellow No. 5, Food RED No.2, Food Blue No.2, etc.), food lakes, red iron oxide, etc.

Examples of the stabilizers include a basic substance in the case of a basic pharmaceutically active ingredient, and an acidic substance in the case of an acidic pharmaceutically active ingredient.

The solid preparation of the present invention can be produced in accordance with a conventional method in the fields of pharmaceutics. Such methods include, for instance, a method which comprises blending, if necessary after addition of water, a pharmaceutically active ingredient, a water-soluble sugar alcohol and low-substituted hydroxypropylcellulose having

hydroxypropoxyl group contents of 7.0 to 9.9 percent by weight, and molding, if necessary followed by drying.

The blending procedure can be carried out by any of the conventional blending techniques such as admixing, kneading, granulating, etc. The blending procedure is carried out, for instance, by using an apparatus such as Vertical Granulator VG10 [manufactured by Powrex Corp.], Universal Kneader [manufactured by Hata Iron Works Co., Ltd.] and fluidized bed granulator LAB-1 and FD-3S [manufactured by Powrex Corp.].

The molding procedure can be carried out, for instance, by tabletting with a pressure of 0.5 to 3 ton/cm^2 by using a single-punch tabletting machine [Kikusui Seisakusho] or a rotary type tabletting machine [Kikusui Seisakusho] when a solid preparation is a tablet.

The drying procedure can be carried out by any of the techniques used commonly in the art, such as vacuum drying, fluidized-bed drying, etc.

The solid preparation of the present invention thus obtained exhibits fast disintegrability or dissolubility in the buccal cavity, and also an appropriate strength of preparation.

The buccal dissolution time of the solid preparation of the present invention (the time for healthy male or female adults to complete disintegration of a solid preparation by buccal saliva) is usually about 5 to about 50 seconds, preferably about 55 to about 40 seconds, more preferably about 5 to about 30 seconds.

The strength of the solid preparation of the present invention (measurement with a tablet hardness tester) is usually about 2 to about 20 kg, preferably about 4 to about 15 kg.

The solid preparation of the present invention can be safely administered orally to mammals such as mice, rats, rabbits, cats, dogs, bovines, horses, monkeys, humans, etc.

While the dosage varies depending on kinds of a pharmaceutically active ingredient, a subject, diseases, etc., the dosage can be selected so that the dosage of the pharmaceutically active ingredient is an effective amount.

For instance, when lansoprazole is employed as a pharmaceutically active ingredient, the solid preparation of the present invention is useful for treatment and prophylaxis of digestive ulcer (e.g., gastric ulcer, duodenal ulcer, anastomotic ulcer, Zollinger-Ellison syndrome, etc), gastritis, reflux esophagitis, etc.; eradication of H. pyroli; suppression of gastrointestinal bleeding caused by digestive ulcer, acute stress ulcer and hemorrhagic gastritis; suppression of gastrointestinal bleeding caused by invasive stress (e.g., stress caused by cerebrovascular disease, head injury, failure of many organs, burn injury of a wide range, which necessitate a large-scale operation necessitating the following intensive management, or intensive care); treatment and prophylaxis of ulcer caused by non-steroidal anti-inflammatory agent; treatment and prophylaxis of gastric hyperacidity and ulcer caused by postoperative stress; administration before anesthesia, etc., and the dosage thereof per an adult (body weight: 60 kg) is 0.5 to 1500 mg/day, preferably 5 to 150 mg/day, as lansoprazole.

When voglibose is employed as a pharmaceutically active ingredient, the solid preparation of the present invention is useful for treatment and prophylaxis of obesity, adiposity, hyperlipemia, diabetes, etc., and

the dosage thereof per an adult (body weight: 60 kg) is 0.01 to 30 mg/day, preferably 0.1 to 3 mg/day, as voglibose. This solid preparation can be administered once a day, or two or three times separately a day.

[Mode of carrying out the invention]

The following Working Examples and Comparative Examples are further illustrative but by no means limitative of the present invention.

The physical properties of the tablets prepared in Working Examples and Comparative Examples were determined by the following test methods.

1) Hardness test

Determination was carried out with a tablet hardness tester [manufactured by Toyama Sangyo, Co. Ltd.]. The test was performed in 10 runs and mean values were shown.

2) Buccal disintegration time

Time for complete disintegration or dissolution only by saliva in the buccal cavity was determined.

[Working Examples]

Working Example 1

A fluidized bed granulator [manufactured by Powrex Corp., LAB-1] was charged with 0.8 g of voglibose, 636.8 g of erythritol [manufactured by Nikken Chemical Co., Ltd.] and 160.0 g of low-substituted hydroxypropylcellulose LH-32 [hydroxypropoxyl group contents of 8.8 %, manufactured by Shin-Etsu Chemical Co., Ltd.], and granulation was carried out while spraying distilled water. The granules were dried and then 2.4 g of magnesium stearate was added. The mixture was tabletted using a rotary type tabletting machine with a punch having a beveled edge, 10 mm in diameter, at a tabletting pressure of 1.5 ton/cm^2, to provide tablets each weighing 400 mg.

The hardness and buccal disintegration time of each tablet thus obtained were 6.1 kg and 27 seconds respectively.

Comparative Example 1

Tablets were produced in the same manner as in Working Example 1 except that low-substituted hydroxypropylcellulose LH-32 was replaced by low-substituted hydroxypropylcellulose LH-31 [HPC group contents of 11.0 % by weight, manufactured by Shin-Etsu Chemical Co., Ltd.].

The hardness and buccal disintegration time of each tablet thus obtained were 8.4 kg and 77 seconds respectively.

Comparative Example 2

Tablets were produced in the same manner as in Working Example 1 except that low-substituted hydroxypropylcellulose LH-32 was replaced by low-substituted hydroxypropylcellulose LH-30 [hydroxypropoxyl group contents of 14.6 % by weight, manufactured by Shin-Etsu Chemical Co., Ltd.].

The hardness and buccal disintegration time of each tablet thus obtained were 6.8 kg and 51 seconds respectively.

[Effects of the invention]

The solid preparation of the present invention possesses excellent disintegrability or dissolubility, and is used for treatment or prophylaxis of various diseases as a preparation capable of buccal disintegration or dissolution which can be administered without water by aged people and children anywhere or anytime,

Further, the solid preparation also possesses an appropriate strength of preparation, and is excellent

in long-term storage stability.

[Document Name] Abstract

[Abstract]

[Problem to solve]

To provide a solid preparation which exhibits excellent buccal disintegration and dissolution and also an appropriate strength

[Solution means]

A solid preparation which comprises (1) a pharmaceutically active ingredient, (2) a water-soluble sugar alcohol, and (3) low-substituted hydroxypropylcellulose having hydroxypropoxyl group contents of 7.0 to 9.9 percent by weight.

[Elected drawings] None